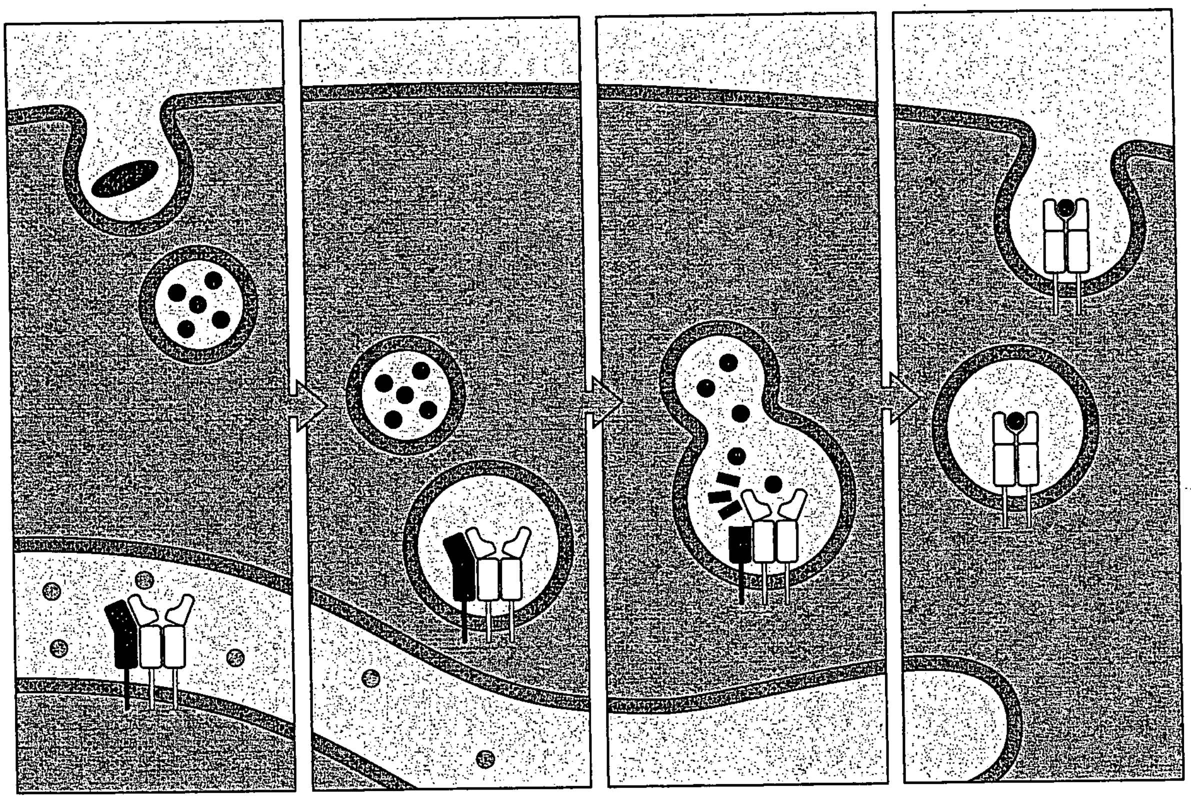
IMMUNO BIOLOGY

THE IMMUNE SYSTEM IN HEALTH AND DISEASE



JANEWAY · TRAVERS

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THE IMMUNE SYSTEM IN HEALTH AND DISEASE

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antibody molecules and is thus known as the **variable region**. The variability of antibody molecules allows each molecule to recognize a particular antigen, and the sum total of all antibodies can bind to virtually any structure. The region of the antibody molecule that engages the effector functions of the immune system does not vary in the same way and is thus known as the **constant region**, although it has in fact five main forms, or **isotypes**, which are specialized for activating different immune effector mechanisms.

The remarkable diversity of antibody molecules is the consequence of a highly specialized mechanism by which the antibody genes expressed in any given cell are assembled by joining two or three of a large number of gene segments to form a variable-region gene during the development of the B cell. Subsequent DNA rearrangement can attach the assembled variable-region gene to any constant-region segment to encode any of the five isotypes.

B cells do not secrete antibody until they have been stimulated by specific antigen, which they recognize by means of membrane-bound immunoglobulin molecules, which serve as antigen receptors. Antigen binding to these surface receptors is a crucial step in inducing the B cell to proliferate and differentiate into an antibody-secreting cell.

In this chapter, we will describe the structural and functional properties of antibody molecules and explain the special genetic processes that generate antibody diversity and produce functional versatility, ending with an account of the mechanisms whereby antigen binding by surface immunoglobulin molecules signals B cells.

The structure of a typical antibody molecule.

All antibodies are constructed in the same way from four polypeptide chains, and the generic term **immunoglobulin** (**Ig**) is used for all such proteins. Within this general class of immunoglobulins, however, five classes of antibodies – IgM, IgD, IgG, IgA, and IgE – can be distinguished biochemically as well as functionally, while more subtle differences confined to the variable region account for the specificity of antigen binding. In this section, we shall describe the general structural features of immunoglobulin molecules using the IgG molecule as an example. In later sections, the DNA rearrangements underlying antibody diversity and functional versatility will be described once the basic features of the antibody molecule are understood.

3-1 IgG antibodies consist of four polypeptide chains.

IgG antibodies are large molecules with a molecular weight of approximately 150 kDa. When they are treated with agents that cleave disulfide bonds, two subunits can be distinguished. One, a polypeptide chain of approximately 50 kDa, is termed the **heavy** or **H chain**, and the other,

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of 25 kDa, is termed the **light or L chain** (Fig. 3.1). The two chains are present in an equimolar ratio, and each intact IgG molecule contains two heavy chains and two light chains [(2 x 50) + (2 x 25) = 150)]. The two heavy chains are linked to each other by disulfide bonds and each heavy chain is linked to a light chain by a disulfide bond. In any one immunoglobulin molecule, the two heavy chains and the two light chains are identical, so the molecule has a two-fold axis of symmetry.

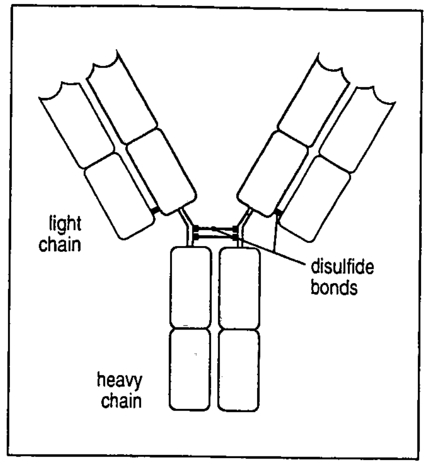

Fig. 3.1 The immunoglobulin molecule has two different polypeptide chains called the heavy chain and the light chain. Each immunoglobulin molecule is made up of two heavy chains (green) and two light chains (yellow) joined by disulfide bridges such that each heavy chain is linked to a light chain and the two heavy chains are linked together.

There are only two types of light chains, which are termed lambda (λ) and kappa (κ) chains. No functional difference has been found between antibodies having λ or κ light chains. For unknown reasons, the ratio of the two light-chain types varies from species to species. In mice, the κ to λ ratio is 20:1, whereas in humans it is 2:1, and in cattle it is 1:20. Distortions in this ratio can sometimes be used to detect immune system abnormalities: for example, an excess of λ light chains in a human might indicate the presence of a λ chain-producing B-cell tumor.

By contrast, there are five main **heavy-chain classes,** often referred to as **isotypes,** and these determine the functional activity of an antibody molecule. The five functional classes of immunoglobulin are **immunoglobulin M (IgM), immunoglobulin D (IgD), immunoglobulin G (IgG), immunoglobulin A (IgA)**, and **immunoglobulin E (IgE)**, and their heavy chains are denoted by the corresponding lower case Greek letter (**μ, δ, γ, α,** and **ε** respectively). Their distinctive functional properties are conferred by the carboxy-terminal half of the heavy chain, where it is not associated with the light chain. We shall describe the distinct heavy-chain isotypes in more detail later. As the general structural features of all the isotypes are similar, we shall consider IgG, which is the most abundant isotype in plasma, as a typical antibody molecule.

3-2 The heavy and light chains are composed of constant and variable regions.

The amino acid sequences of many immunoglobulin heavy and light chains have been determined and show that each chain contains distinct subregions, each about 110 amino acids in length. The light chains have two subregions, while the heavy chain of the IgG antibody has four. All the subregions share patterns of amino acid sequences, suggesting that the immunoglobulin chains have evolved by repeated duplication of an ancestral gene corresponding to one subregion. As we shall see, the individual subregions correspond to separate domains in the folded protein.

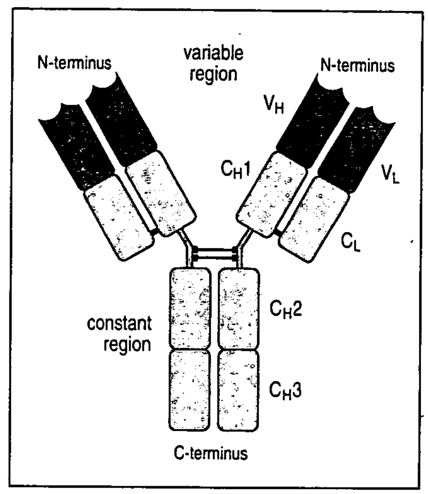

Fig. 3.2 The heavy and light chains of an immunoglobulin can be divided into subregions, or domains, on the basis of sequence similarity. The amino-terminal domain (N-terminus; red) of each chain is variable in sequence when several antibodies are compared; the remaining domains are constant (blue). The two domains of the light chains are termed V_L and C_L. The four domains of the heavy chains are termed V_H, C_H1, C_H2 and C_H3.

Comparison of the sequences obtained for individual antibody molecules reveals that the amino-terminal sequences of both the heavy and light chains vary greatly between different antibodies. The variability in sequence is limited to the first 110 amino acids, corresponding to the first subregion, while the carboxy-terminal sequences are constant between immunoglobulin chains, either light or heavy, of the same isotype (Fig. 3.2). The variable subregions are termed **V regions** or **V domains** and the constant subregions are termed **C regions** or **C domains**.